

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
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| Date of mailing (day/month/year) 06 May 1999 (06.05.99) | |
| International application No. PCT/GB98/02820 | Applicant's or agent's file reference PHM 70275/WO |
| International filing date (day/month/year) 17 September 1998 (17.09.98) | Priority date (day/month/year) 23 September 1997 (23.09.97) |
| Applicant KOROPATNICK, Donald, James et al | |

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

23 March 1999 (23.03.99)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Lazar Joseph Panakal Telephone No.: (41-22) 338.83.38 |
|---|--|

PATENT COOPERATION TREATY

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REC'D 08 DEC 1999

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | | |
|---|--|--|---|
| Applicant's or agent's file reference PHM70275/WO | FOR FURTHER ACTION | | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/GB98/02820 | International filing date (day/month/year) 17/09/1998 | Priority date (day/month/year) 23/09/1997 | |
| International Patent Classification (IPC) or national classification and IPC C12N15/11 | | | |
| Applicant ZENECA LIMITED et al. | | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> | | | |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input checked="" type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application | | | |

| | |
|---|---|
| Date of submission of the demand 23/03/1999 | Date of completion of this report 02.12.99 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Heimann-Pohl, B Telephone No. +49 89 2399 8713 |



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/02820

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-27 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
 - copy of the earlier application whose priority has been claimed.
 - translation of the earlier application whose priority has been claimed.
2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/02820

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- all parts.
- the parts relating to claims Nos. .

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/02820

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------|---------------------|
| Novelty (N) | Yes: | Claims 3,4,7 |
| | No: | Claims 1,2,5,6,8-10 |
| Inventive step (IS) | Yes: | Claims 3,4 |
| | No: | Claims 7 |
| Industrial applicability (IA) | Yes: | Claims 1-8, 10 |
| | No: | Claims |

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/02820

1). The present application relates to antisense oligonucleotides which hybridize to a target nucleic acid sequence in thymidylate synthase (TS) and which

(I) selectively inhibit TS production in mammalian cells (oligo 86 targeted to the 3' end of TS mRNA, including the translation stop site and oligo 83 targeted to a sequence in the 3' untranslated region)

(II) selectively enhance TS production in mammalian cells (oligo 91 and 93 targeted to the TS mRNA translation start site at the 5' end).

Furthermore, the application relates to combination products comprising an antisense oligonucleotide targeted to TS in combination with an anticancer agent and uses thereof in pharmaceutical compositions and methods for treatment of cancer.

2). Prior art.

D1 (Ju J. : "Increased Drug Sensitivity of Tumor Cells by Manipulation of Cell Cycle Control Genes, 1996, Thesis University of Southern California, pages 100-130) addresses the problem of treating cancer with chemotherapy that the response among individuals with the same type of tumor to the same treatment is rather variable. Furthermore, in response to some drugs (5-FU) cells often adapt to the drug, i.e. acquire resistance, by increasing the expression of the target enzyme (TS). D1 discloses that upon antisense vector transfection chemosensitivity to fluoropyrimidines was increased in cancer cells. However, antisense oligo DA44 which is directed to the translational start site decreases chemosensitivity to FdUrd.

D2 (WO A 98 49287) addresses the problem of preventing or overcoming resistance to thymidylate synthase inhibitor compounds in tumor cells. The solution is based on the use of antisense oligonucleotides (SEQ ID NO 1 and 2) targeted to the translational start region of TS and which inhibit the expression of TS protein. Other preferred regions include the 3' UTR region, the translational stop site and splice junction sites. Further D2 relates to combination products

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/02820

comprising the antisense oligonucleotide in combination with anticancer agents and methods for treatment of cancer.

D3 (EP A 0 290 144) discloses oligos for PCR of the TS gene, the oligo primer complementary to DNA bases -3 to +23 corresponds to oligos 91 and 92 of the present application.

3). Novelty

Due to the rather broad and imprecise wording of claims 1, 2, 5, 6 and 8-10 these claims embrace the subject matter disclosed in D1 and D2. Consequently these claims lack novelty (Art. 33 (2) PCT).

The antisense oligonucleotides of claims 3 and 4 and the combination product of claim 7 appear to be novel with regard to 1 and D2.

4). Inventive Step

The underlying problem of the present application was already addressed by D1 and D2 which are regarded as closest prior art (§ 2). above). However, studying D1 and D2 it appears that the results achieved with the antisense oligonucleotides targeted to the translational start site are contradictory. Therefore the specific sequences of claims 3 and 4 do not appear obviously derivable from D1 even if combined with D3 because the specific effect of each oligonucleotide did not appear to be predictable with regard to the controversy in D1 alone and also between D1 and D2.

However, claim 7 is not directed to a specific novel and inventive oligonucleotide. The use of a specific prior art anticancer agent in said claim does not confer an inventive step to the combination product since it is not an inventive choice. The combination product of claim 7 lacks an inventive step (Art. 33 (3) PCT).

5). Industrial Applicability

For the assessment of the present claim 9 on the question whether they are

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/02820

industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6). Priority

If the priority is not valid which could not be checked then other documents cited in the International Search Report will become relevant.

7). Non-Unity

The present application apparently addresses two different problems.

Problem I is related to the acquired resistance of tumor cells to anticancer agents including Tomudex and 5-FU (page 2 of the description).

The solution are oligonucleotides which selectively inhibit TS production in mammalian cells (oligo 86 targeted to the 3' end of TS mRNA, including the translation stop site and oligo 83 targeted to a sequence in the 3' untranslated region).

Problem II is related to conferring resistance to the toxic effect of anticancer agents in human cells.

The solution are oligonucleotides which selectively enhance TS production in mammalian cells s (oligo 91 and 93 targeted to the TS mRNA translation start site at the 5' end).

The two problems and their solutions are not so linked as to form a single general inventive concept (Rule 13.1 PCT).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/02820

- 8). The Sequence Listing is part of the description and was taken into consideration.

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(PCT Article 36 and Rule 70)

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| | No: | Claims 7 |
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International application No. PCT/GB98/02820

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

8). The Sequence Listing is part of the description and was taken into consideration.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) PHM 70275/WO

Box No. I TITLE OF INVENTION

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the residence indicated in this Box is the applicant's State (that is, country) of residence if no State residence is indicated below.)

ZENECA Limited
15 Stanhope Gate
London
GB-W1Y 6LN
GB

This person is also inventor.

Telephone No.
(01625) 516173

Faxsimile No.
(01625) 583358

Telex/Teletypewriter No.
669095/669388

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the residence indicated in this Box is the applicant's State (that is, country) of residence if no State residence is indicated below.)

ISIS Pharmaceuticals
2292 Faraday Avenue
Carlsbad
California, 92008
USA

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: agent common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

TAIT, Brian Steele
Intellectual Property Department
ZENECA Pharmaceuticals
Mereside, Alderley Park
Macclesfield, Cheshire, GB-SK10 4TG
GB

Telephone No.

(01625) 514151

Faxsimile No.

(01625) 583358

Telex/Teletypewriter No.

669095/669388 ZENPHAG

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KOROPATNICK, Donald James
London Regional Cancer Centre
790 Commissioners Road East
London
Ontario
Canada
N6A 4L6

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

CANADIAN

State (that is, country) of residence:

CANADA

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

VINCENT, Mark David
London Regional Cancer Centre
790 Commissioners Road East
London
Ontario
Canada
N6A 4L6

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

CANADIAN/BRITISH

State (that is, country) of residence:

CANADA

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DEAN, Nicholas Mark
ISIS Pharmaceuticals,
2292 Faraday Avenue
Carlsbad
California, 92008
USA

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

BRITISH

State (that is, country) of residence:

USA

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated in another continuation sheet.

No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input type="checkbox"/> GW Guinea-Bissau | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| <input checked="" type="checkbox"/> LR Liberia | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

-
-

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

See Notes to the request form

No. VI PRIORITY CLAIM

 Further priority claim(s) are indicated in the Supplemental Box.

| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: | | |
|---|----------------------------------|----------------------------------|--|--|
| | | national application: country | regional application: regional Office | international application: receiving Office |
| item (1) 23-SEP-1997 (23.09.97) | 9720107.3 | GB | | |
| item (2) 17-OCT-1997 (17-10-97) | 9722012.3 | GB | | |
| item (3) 06-JUN-1998 (06-JUN-98) | 9812140.3 | GB | | |

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): item (1), (2), (3)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

| | |
|--|--|
| Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the International search, indicate the Authority chosen; the two-letter code may be used): | Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): |
|--|--|

Date (day/month/year) Number Country (or regional Office)

ISA /

Box No. VIII CHECK LIST; LANGUAGE OF FILING

| | |
|---|--|
| This international application contains the following number of sheets: | This international application is accompanied by the item(s) marked below: |
| request : 4 | 1. <input checked="" type="checkbox"/> fee calculation sheet |
| description (excluding sequence listing part) : 26 | 2. <input type="checkbox"/> separate signed power of attorney |
| claims : 2 | 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: |
| abstract : 1 | 4. <input type="checkbox"/> statement explaining lack of signature |
| drawings : 13 | 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): |
| sequence listing part of description : 5 | 6. <input type="checkbox"/> translation of international application into (language): |
| Total number of sheets : 51 | 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material |
| | 8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form |
| | 9. <input type="checkbox"/> other (specify): |

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: BRITISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Brian S. Tait

Brian Steele TAIT
AGENT FOR APPLICANT

For receiving Office use only

| | |
|---|--|
| 1. Date of actual receipt of the purported international application: | 2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: | |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2): | |
| 5. International Searching Authority (if two or more are competent): ISA / | 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid. |

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

INTERNATIONAL COOPERATION TREATY

PCT**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference PHM 70275/W0 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/GB 98/ 02820 | International filing date (day/month/year) 17/09/1998 | (Earliest) Priority Date (day/month/year) 23/09/1997 |
| Applicant ZENECA LIMITED et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

ANTISENSE OLIGONUCLEOTIDES AGAINST THYMIDYLATE SYNTHASE

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/02820

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02820

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 C07H21/02 A61K31/70 A61K31/505 //C07D239/95,
C12N9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | JU J.: "INCREASED DRUG SENSITIVITY OF TUMOR CELLS BY MANIPULATION OF CELL CYCLE CONTROL GENES" 1996, THESIS UNIVERSITY OF SOUTHERN CALIFORNIA, PAGE(S) 100 - 130 XP002081365 see the whole document | 1, 2, 5, 6, 8-10 |
| Y | EP 0 290 144 A (CITY OF HOPE) 9 November 1988 see page 3, column 1, line 30 - line 39 | 3, 4 7 |
| E | WO 98 49287 A (HYBRIDON INC) 5 November 1998 see abstract see page 8; table 1 see claims 1, 24 | 1, 2, 5, 6, 8-10 |
| | --- | -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

25 February 1999

Date of mailing of the international search report

10/03/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Galli, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02820

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| P, X ✓ | <p>FERGUSON P.J. ET AL: "Enhancement of Tomudex cytotoxicity by an antisense oligonucleotide against thymidylate synthase mRNA". PROCEEDINGS OF THE 89TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW ORLEANS, MARCH 28-APRIL 1, 1998, VOL. 39, PAGE 416, ABSTRACT 2831 XP002094749 see abstract</p> <p>---</p> | 1,2,5-10 |
| P, Y ✓ | <p>WO 98 33518 A (SLOAN KETTERING INST CANCER ; TONG YOUZHI (US); LIU CHEN XINYUE (US) 6 August 1998 seq ID 37</p> <p>-----</p> | 4 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02820

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|-----------|------------------|
| EP 0290144 A | 09-11-1988 | AU | 1556188 A | 10-11-1988 |
| | | JP | 1055199 A | 02-03-1989 |
| | | US | 5736326 A | 07-04-1998 |
| | | US | 5585363 A | 17-12-1996 |
| | | US | 5166140 A | 24-11-1992 |
| | | US | 5814489 A | 29-09-1998 |
| WO 9849287 A | 05-11-1998 | AU | 7364998 A | 24-11-1998 |
| WO 9833518 A | 06-08-1998 | NONE | | |